my copy

October 8, 1946.

Dear Dr. Lwoff:

We hope and trust that you had a pleasant journey back to France, and that things are well with you there.

This letter is primarily to ask you whether it would be possible to obtain phages active on Proteus strains. I believe you mentioned such during our conversation in New Haven. We have not yet isolated mutants from Proteus strains, so that we are not yet in a position to assess the significance of the 'large bodies' upon which Dienes reported. He told me last week that he has been making single-large-body isolations, but that so far there is found only a single 'mating type' in the progeny of a single large body. He is also undertaking a serological examination.

The work with Escherichia coli has made no large progress since you visited these laboratories. I regret we have not yet had opportunity to make single cell isolations of the prototrophs obtained in mixed cultures. However, by ultra-violet treatment of a prototroph, we have been able to pick up a new mutant (nicotinicless) which is further evidence that they are indeed new types. We are attempting to rule out transformation as completely as possible. We have been unable to find any effects of sterile filtrates of one mutant on another. The types which we isolated at about the time of your visit here, which have double requirements, one from each of the parental strains, are of course significant in that regard. Examination of the relative proportions of different types indicates that there is not an entirely random segregation of characters, but that linkages, or other restrictions, may be operating. For example, when one of the parents is phage resistant in a certain cross, about 25% of the prototrophs are resistant; when the other parent is resistant, about 75% of the prototrophs are resistant. We have gotten this very suggestive result in several combinations that have been tried, but the situation requires further analysis, of course.

While we are by no means abandoning our work on E. coli, we are beginning now to study other organisms, particularly Salmonella. Also we might be interested to repeat Valentine and Rivers' experiments (J. Exp. Med. 45:993, 1927- finding this reference was rather difficult) with Hemophilus. However, we have not been able to obtain any H. canis strains here. Would you be so kind as to send us cultures of canis and of parainfluenzae? We should however be equally delighted to hear that you were interested in performing such an experiment, in view of our inexperience with these organisms. While we do not foresee any immediate application, this time might be appropriate to ask for Moraxella, and for the Coli-mutabile strain that has been used in your laboratories (coli-lwoffi?). If there is any way in which we can reciprocate, please do not hesitate to inform us.

Finally, I should like to request a favor. Would you transmit our respects to Dr. Boivin, and the following message: we are most interested in his recent investigations, and would appreciate any publications or details that he might care to send. In particular, we are interested in whether there is indication that transformation might be accomplished in both directions: are the rough cells in C2-S cultures treated with C1-S filtrates to be accounted for as spontaneous mutants, or is their

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occurrence dependent on the transforming factors. Does Dr. Boivin believe that the transformations from C2-S to C1-S occur directly, or via the C2-R? We are not clear on whether transformations from C1 to C2 occur with any regularity, and if when they occur, they also involve the loss of the ability to ferment sucrose, nor as to the enzymatic characteristics of the rough strains. We hope these queries are not too burdensome; they will no doubt be mentioned in later publications, but because of the obvious bearing on our work, we would appreciate an indication as to what is the case.

In addition to the tests made on filtrates, mentioned above, we have attempted to obtain prototrophs from mixtures of a double mutant with another mutant which had been sterilized (not entirely) with ultra-violet light. Since a small proportion of cells were still alive, it might be expected that any transforming principle would still be largely intact. However, no prototrophs were obtained, indicating that transformation does not occur, and even that those cells which were still viable did not participate in the recombination process.

Attempts to improve the conditions (cultural) for recombination have not been startlingly successful, although the best medium so far that we have tried is 'Yeast Beef Broth' (Difco). Any rich medium well buffered at ca. 7 and without too much fermentable sugar would undoubtedly suffice. Attempts to increase recombination rates by the use of starved cultures, and that sort of thing have failed, as has the use of penicillin which leads to the appearance of so-called 'Zygospores' in the culture. We extend this information in case you should desire to proceed with similar experiments on material of your own choice.

Please extend my regards to Dr. Monod, and be assured of Dr. Tatum's felicitations as well.

Sincerely yours,

Joshua Lederberg.